PATENT SPECIFICATION

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COMPLETE SPECIFICATION

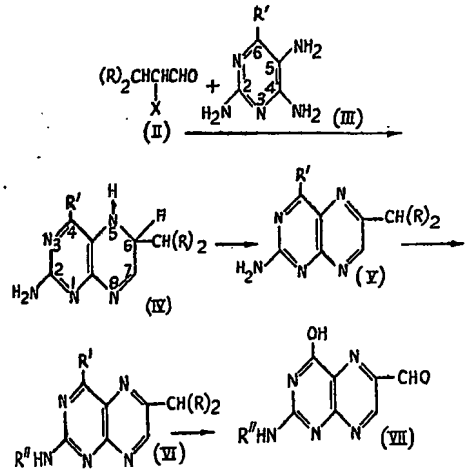
Substituted Pteridine Derivatives

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to substituted pteridine derivatives. In brief, this invention provides novel 2-amino-and 2-acylamino pteridines with substituents in the 4- and 6-positions and having one of the general formulae V, VI and VII below. The novel compounds may be obtained from the 2-halo-3,3 - di-(alkoxy or aralkoxy)-propionaldehydes which are claimed and may be prepared by the process described and claimed in the specification of our copending Application No. 2842/54 (Serial No. 785,351).

In accordance with the present invention, the said substituted propionaldehyde (Formula II below) is condensed with a 2,4,5-triamino-6-(hydroxy, alkoxy, aryloxy, or aralkoxy)-pyrimidine (Formula III) to produce a 2-amino-5,6-dihydropteridine of the Formula IV below, which is oxidized to remove the 5- and 6-hydrogen atoms and produce a compound of Formula V below. This compound can be acylated to produce a compound of general formula VI, which may then be hydrolysed to a 2-acylamino-4-hydroxy-6-formyl pteridine (VII).

The reactions referred to above and the formulae of the various compounds are shown in the following reaction scheme, in which X is a halogen, R is an alkoxy or aralkoxy radical, R^1 is a hydroxy, alkoxy, aryloxy, or aralkoxy radical, and R^{11} is an acyl radical



The novel compounds of formula VII are useful as starting materials for the process described and claimed in the specification of our copending Application No. 18455/56 (Serial No. 785,354) for producing N-{*p*-[(2-acylamino-4 - hydroxy-6 - pteridylmethylene) imino]benzoyl} glutamic acids, which can be readily converted in good yields to pteroylglutamic acid, otherwise called vitamin B_c, by certain of the processes described and claimed in the specification of our copending Application No. 18456/56. (Serial No. 785,355). The novel compounds of formula VI and VII are also readily converted to pteroylglutamic acid by certain of the processes described and claimed in the specification of our copending Application No 18456/56 (Serial No. 785,355).

The pteridine moiety, which is an essen-

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[*Price 3s. 6d.*]

tial structural unit of pteroylglutamic acid, is produced by condensing a 2-halo-3,3-(dialkoxy or diaralkoxy)-propionaldehyde with a 2,4,5-triamino pyrimidine having in the 6 position a hydroxy, alkoxy, aryloxy, or aralkoxy radical to produce the corresponding 2-amino-6-(dialkoxymethyl or diaralkoxymethyl)-5,6-dihydropteridine. Fortunately, the resulting pteridine moiety is practically all the 6-methyl position isomer needed in the synthesis of biologically active compounds such as pteroylglutamic acid. The condensation is preferably effected by intimately contacting the reactants in the presence of a solvent and a condensing agent. The solvent can be water or an inert organic solvent or mixture of such solvents. Illustrative of solvents which can be used are hydroxylated solvents such as alcohols and glycols, particularly ethyl alcohol and ethylene glycol, and solvents such as acetone, benzene, and formamide. Examples of condensing agents which can be used are sodium acetate, disodium phosphate, silver carbonate, and sodium formate. The reaction will proceed at ordinary temperatures but the rate of reaction may be increased by using elevated temperatures such as 60—65° C.

The condensation resulting in formation of the pteridine nucleus proceeds satisfactorily regardless of the substituent in the 6 position of the 2,4,5-triamino pyrimidine used as reactant. Thus, equally good results are obtained when the 6-substituent is hydroxy, an alkoxy radical such as ethoxy, propoxy or butoxy, an aryloxy radical such as phenoxy, or an aralkoxy radical such as benzyloxy. However, the condensation is most easily accomplished when a 2-(bromo or chloro)- 3,3-(dialkoxy or diaralkoxy)-propionaldehyde is used. In specific embodiments of this condensation 2-amino-4-benzyloxy - 6 - diethoxymethyl-5.6-dihydropteridine and 2-amino-4-hydroxy-6-diethoxymethyl-5,6-dihydropteridine can be produced by condensing respectively 2,4,5-triamino-6-benzyloxy pyrimidine and 2,4,5 - triamino-6-hydroxy pyrimidine with 2-bromo-3,3-diethoxy propionaldehyde in the presence of aqueous ethanol and sodium acetate. After completion of the condensation the desired product can be recovered from the reaction mixture by conventional procedures or the reaction mixture can be used directly in the preparation of the fully aromatic pteridine moiety.

The fully aromatic 2-amino pteridines having a hydroxy, alkoxy, aryloxy, or aralkoxy radical in the 4 position and a dialkoxymethyl or diaralkoxymethyl radical in the 6 position can be prepared by dehydrogenation of the correspondingly substituted 5,6-dihydropteridines. The dehydrogenation is readily accomplished by intimately contacting the 5,6-dihydropteridine with a mild oxidizing agent. Specific examples of suitable oxidizing agents are air, oxygen, iodine, and hydrogen peroxide with a ferrous salt. In general, it is preferable to maintain a pH of about 8 to 9 to obtain best results. In addition, the reaction is conveniently accomplished in a suitable inert solvent such as alcohols, glycols, acetone benzene, formamide, dioxane, and water. The resulting pteridines can be isolated from the reaction mixture by conventional methods. According to specific applications of this dehydrogenation reaction, 2-amino-4-benzyloxy-6-diethoxymethyl pteridine and 2-amino-4-hydroxy-6-diethoxymethyl pteridine are produced by oxidizing respectively 2-amino-4-benzyloxy-6-diethoxymethyl - 5,6-dihydropteridine and 2-amino-4-hydroxy-6-diethoxymethyl-5,6-dihydropteridine with hydrogen peroxide and ferrous sulphate in a suitable solvent. Examples of other representative pteridines which can be prepared in this manner are 2-amino-4-butoxy-6-dibenzyloxymethyl pteridine, 2-amino-4-ethoxy-6-dimethoxymethyl pteridine, and 2-amino-4-methoxy-6-dipropoxymethyl pteridine.

In the next step of the process 2-amino pteridines containing a hydroxy, alkoxy, aryloxy, or aralkoxy substituent in the 4 position and a dialkoxymethyl or diarylkoxymethyl substituent in the 6 position are converted to the corresponding novel 2-acylamino pteridines. The acylation can be effected by intimately contacting the substituted 2-amino pteridines with a suitable acylating agent such as an acyl halide or carboxylic acid anhydride. Acetyl chloride, propionyl chloride, butyryl chloride, benzoyl bromide, acetic anhydride, propionic anhydride, butyric anhydride, and benzoic anhydride are examples of suitable acylating agents. The acylation is conducted in a liquid reaction medium which can be an inert organic solvent or an excess of the acylating agent. In general, an added solvent is not required since the acylating agents are usually liquids at normal or slightly elevated temperatures. Although the reaction proceeds at ordinary temperatures it is usually effected at higher temperatures such as the reflux temperature to enhance the rate of reaction. The desired 2-acylamino pteridine can be isolated from the reaction mixture by conventional methods such as cooling and filtering to separate the crystalline product. According to this acylation procedure, 2-acylamino pteridines having the described substituents in the 4 and 6 positions can be readily prepared in which the acyl substituent is an alkyl, aryl, or aralkyl carbonyl radical. Thus, some specific 2-acylamino pteridines which can be produced according to this process are 2-propionamido-4 - benzyloxy - 6 - dimethoxymethyl pteridine, 2-butyramido-4 - hydroxy-6 - dipropoxymethyl pteridine, 2-acetamido-4-phenoxy-6-diethoxymethyl pteridine, 2-acetamido-4-hydroxy-6-diethoxymethyl pteridine, 2-benzamido-4-hydroxy - 6 - diethoxymethyl pteridine, and 2-phenylacetamido-4-hydroxy-6-diethoxymethyl pteridine.

The acylated pteridines possess unique and valuable properties which distinguish them from the non-acylated pteridines. For example, the non-acylated pteridines reported in the art are amorphous compounds which are nearly insoluble in ordinary solvents. Therefore it was indeed surprising to discover that acylated pteridines, and derivatives of acylated pteridines could be readily produced in crystalline form. Furthermore, the acylated pteridines were found to have an unexpectedly high solubility in water and many organic solvents. The ability to produce crystalline compounds with high solubility by the introduction of an acyl group on the 2-amino was entirely unexpected since pteridines having such desirable properties were heretofore unkown. This combination of desirable properties greatly enhances the usefulness of the 2-acylamino pteridines. Thus, the production of crystalline pteridines is a great aid in the purification of such compounds. Because of their greater solubility, the 2-acylamino pteridines can be used in reactions with smaller volumes of solvents than the non-acylated compounds, thereby allowing a saving in material and permitting greater manipulative freedom.

In the next step of the process, 2-acylamino pteridines substituted in the 4 position with a hydroxy, alkoxy, aryloxy, or aralkoxy radical and in the 6 position with a dialkoxymethyl or diaralkoxymethyl radical are hydrolysed with acid to the corresponding 2-acylamino-4-hydroxy-6-formyl pteridine. According to this hydrolysis reaction the acetal radical in the 6 position is converted to a formyl radical. Simultaneously pteridines which contain an alkoxy, aryloxy, or aralkoxy radical in the 4 position are hydrolysed to the corresponding 4-hydroxy pteridines. Either mineral or organic acids can be used for the hydrolysis. Examples of some suitable acids are hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, and formic acid. The reaction is readily conducted in a solvent medium which can be an excess of the acid used or an added solvent such as water, or an inert organic solvent. Normal or somewhat elevated temperatures may be used to promote the reaction. After the hydrolysis has been completed crystalline 2 - acylamino-4-hydroxy-6-formyl pteridine is isolated by conventional methods. In specific applications of this reaction 2-acetamido-4-hydroxy-6-diethoxymethyl pteridine and 2-propionamido-4-benzyloxy-6-methoxymethyl pteridine are hydrolysed with formic acid to 2-acetamido-4-hydroxy-6-formyl pteridine and 2-propionamido-4-hydroxy-6-formyl pteridine. Other similar compounds which can be prepared in this manner are 2-benzamido-4-hydroxy-6-formyl pteridine, 2-butyramido-4-hydroxy-6-formyl pteridine and 2-phenylacetamido-4-hydroxy-6 - formyl pteridine.

The following examples illustrate the processes of the present invention.

EXAMPLE 1.

Production of 2-amino-4-benzyloxy-6-diethoxymethyl-5,6 - dihydropteridine and 2-amino-4 - benzyloxy - 6 - diethoxymethyl pteridine.

To a solution of 5 gm. of 2-bromo-3,3-diethoxy-propionaldehyde in 70 ml. of ethanol was added a solution of 2,4,5-triamino-6-benzyloxy-pyrimidine in 70 ml. of ethanol containing 2 gm. of sodium acetate. The solution was stirred at room temperature for 15 minutes and subsequently heated at 60—65° C. for 90 minutes. The reaction mixture was cooled to room temperature and added to 700 ml. of water with stirring to prepare for purification of the product.

To the resulting slurry 2.5 *N* hydrochloric acid was added until the mixture became acidic. Insoluble matter that formed was removed by filtration. After cooling, the filtrate was added to an excess of 6 *N* ammonium hydroxide at a temperature of 5—10° C. The amorphous precipitate was removed by filtration and dried. The yield of 2-amino-4-benzyloxy-6-diethoxymethyl - 5,6-dihydropteridine was 3.5 gm.

A sample was purified further by dissolving it in ethyl acetate and adding *n*-hexane until the product precipitated.

To an ethanolic solution of 2-amino-4-benzyloxy-6-diethoxymethyl - 5,6 - dihydropteridine was added 50 mg. of ferrous sulphate in 1 ml. of water and then 2.3 gm. of 30% hydrogen peroxide in 10 ml. of water was added over a 30 minute period. The mixture was concentrated under reduced pressure to a small volume and 2.5 *N* hydrochloric acid added to dissolve most of the oil. The solution was separated from insoluble material by decantation and added to an excess of cold 6 *N* ammonium hydroxide. A precipitate resulted which was isolated and dried. The yield of 2-amino-4-benzyloxy-6 - diethoxymethyl pteridine was 4 gm. and its ultraviolet absorption spectrum in 0.1 *N* NaOH had maxima at 2560 Å (E% = 369) and 3610 Å (E% = 210); in 0.1 *N* HCl it had a maximum at 3350 Å (E% = 364).

By a paper-strip chromatography of the acid obtained by permanganate oxidation of 2-amino-4-hydroxy-6-formyl pteridine which was produced by acetal hydrolysis of 2-amino-4-benzyloxy-6-diethoxymethyl pteridine, it was found that the product was all the desired 6-isomer.

The solution of 2-amino-4-benzyloxy-6-diethoxymethyl-5,6-dihydropteridine used in this example was prepared by reacting 4.6 gm. of 2,4,5-triamino-6-benzyloxy pyrimidine and 1.8 gm. of sodium acetate in 63 ml. of ethanol with 4.5 gm. of 2-bromo-3,3-diethoxy-propionaldehyde in 63 ml. of ethanol.

EXAMPLE 2.

Production of 2-amino-4-hydroxy - diethoxymethyl-5,6-dihydropteridine and 2-amino-4-hydroxy-6-diethoxymethyl pteridine.

5.0 gm. of 2,4,5-triamino-6-hydroxy pyrimidine sulphate was dissolved in 140 ml. of water containing 5 gm. of barium chloride. The solution was heated to 60° C. in a nitrogen atmosphere for 1 hour with stirring and subsequently filtered hot to remove the insoluble precipitate.

To the resulting solution of 2,4,5-triamino-6-hydroxy pyrimidine was added 140 ml. of ethanol and then 5.14 gm. of 2-bromo-3,3-diethoxy-propionaldehyde. The reaction mixture was stirred under nitrogen at room temperature for 56 hours to yield a solution of 2-amino-4-hydroxy-6 - diethoxymethyl - 5,6-dihydropteridine. The solution was then adjusted to pH 8—9 and 50 mg. of ferrous chloride and 2.6 gm. of 30% hydrogen peroxide added at room temperature. The solution was stirred for 5 hours, filtered, and the precipitate washed with water, alcohol, and ether to yield purified 2-amino-4-hydroxy-6-diethoxymethyl pteridine.

A sample was purified by conversion to the sodium salt and reprecipitation of the original free base. It had an ultraviolet absorption curve which exhibited maxima in 0.1 *N* HCl at 3180 Å (E% = 340) and in 0.1 *N* NaOH at 2550 Å (E% = 941), 3620 Å (E% = 288).

In a similar manner, 2-amino-4-hydroxy-6-diethoxymethylpteridine was prepared by reacting 2-chloro-3,3 - diethoxy - propionaldehyde with 2,4,5-triamino-6-hydroxy - pyrimidine in ethanol and in the presence of sodium acetate to produce 2-amino-4-hydroxy-6 - diethoxymethyl - 5,6 - dihydropteridine which was oxidized with hydrogen peroxide and ferrous sulphate to 2-amino-4-hydroxy-6-diethoxymethyl pteridine.

EXAMPLE 3.

Production of 2-amino-4 - hydroxy - 6 - dibenzyloxymethyl-5,6-dihydropteridine and 2 - amino-4-hydroxy-6 - dibenzyloxymethyl pteridine.

After passing nitrogen through a stirred solution of 8.2 gm. of sodium acetate in a mixture of 200 ml. of ethanol for 30 minutes, 4.7 gm. of 2,4,5-triamino-6-hydroxy - pyrimidine dihydrochloride and 7.0 gm. of 2-bromo-3,3-dibenzyloxy-propionaldehyde were added to the solution. The reaction mixture was stirred overnight at room temperature, forming 2-amino-4-hydroxy-6 - dibenzyloxymethyl - 5,6 - dihydropteridine in solution. About 0.1 gm. of ferrous sulphate was dissolved in 3 ml. of water and added to the reaction mixture together with 30 gm. of 10% hydrogen peroxide added dropwise. The reaction mixture was filtered after standing overnight to give 2-amino-4-hydoxy-6-dibenzyloxymethyl pteridine which is readily purified by preparation of its sodium salt and reprecipitation of the free base.

EXAMPLE 4.

Production of 2-acetamido-4-hydroxy-6-diethoxymethyl pteridine.

To a 3-necked flask equipped with stirrer and reflux condenser was added 4.2 gm. of 2-amino-4-hydroxy-6-diethoxymethyl pteridine and 80 ml. of acetic anhydride. The mixture was refluxed with stirring for 1.5 hours. To the solution was added 2 gm. of activated carbon and refluxing was continued for 10 minutes. The hot solution was filtered and cooled in the ice-box overnight. The crystalline precipitate which formed was filtered and washed with 10 ml. of cold acetic anhydride and then with ether. The precipitate was dried at 50° C. under reduced pressure to yield white crystalline 2-acetamido-4-hydroxy-6-diethoxymethyl pteridine. A 1 gm. sample of the product was recrystallized from 2 ml. of dioxane and melted at 198—200° C.

The ultraviolet absorption curve exhibited maxima in 0.1 *N* HCl at 2330 Å (E% = 448), 2820 Å (E% = 380), and 3300 Å (E% = 332), and in 0.1 *N* NaOH at 2560 Å (E% = 782) and 3500 Å (E% = 227).

EXAMPLE 5.

Production of 2-propionamido-4-hydroxy-6-diethoxymethyl pteridine.

A slurry of 3.5 gm. of 2-amino-4-hydroxy-6-diethoxymethyl pteridine in 70 gm. of propionic anhydride was heated at 140° C. for five hours during which time solution was effected. To the reaction mixture was added 1.5 gm. of charcoal and the mixture filtered. The filtrate was evaporated to about one-half volume and allowed to stand overnight in the cold. The solid was collected by filtration, washed twice with ethyl ether and twice with petroleum ether. After drying in air the light-tan crystals of 2-propionamido-4-hydroxy-6-diethoxymethyl pteridine weighed 2.95 gm.

EXAMPLE 6.

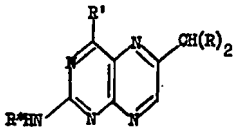
Production of 2-acetamido-4-hydroxy-6-formyl pteridine.

To a flask equipped with a stirrer was added 860 ml. of 98% formic acid and 58 gm. of 2-acetamido-4 - hydroxy-6 - diethoxymethyl pteridine. Complete solution was achieved in 5 minutes. Upon standing for 15 minutes at room temperature a precipitate appeared. The solution was allowed to stand under nitrogen in an ice-box overnight. It was filtered and the precipitate was washed with cold formic acid and then anhydrous ether giving 2-acetamido-4-hydroxy-6-formyl pteridine.

The ultraviolet absorption curve exhibited maxima in 0.1 *N* HCl at 2325 Å (E% = 488), shoulder 2900—3000 Å (E% = 443), and 3250 Å (E% = 502) and in 0.1 *N* NaOH at 2550 (E% = 594), 2760 Å (E% = 434) and 3650 Å (E% = 394).

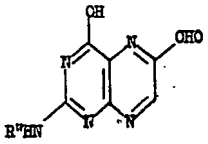
What we claim is:—

1. A compound having the formula:



in which R is an alkoxy or aralkoxy radical, R^1 is a hydroxy, alkoxy, aryloxy, or aralkoxy radical and R* is an acyl radical or a hydrogen atom.

2. A compound having the formula:



in which R^{11} is an acyl radical.

3. 2-amino-4-hydroxy-6 - diethoxymethyl-pteridine.

4. 2-amino - 4 - hydroxy-6 - dibenzyloxy-methyl-pteridine.

5. 2-acetamido-4 - hydroxy - 6 - diethoxy-methyl-pteridine.

6. 2-propionamido-4-hydroxy-6 - diethoxy-methyl-pteridine.

7. 2-acetamido-4 - hydroxy - 6 - formyl-pteridine.

8. 2-propionamido-4-benzyloxy-6 - dimeth-oxymethyl pteridine.

9. 2-butyramido-4-hydroxy-6 - dipropoxy-methyl pteridine.

10. 2-acetamido-4-phenoxy - 6 - diethoxy-methyl pteridine.

11. 2 benzamido-4-hydroxy-6-formyl pter-idine.

12. 2-phenylacetamido-4-hydroxy-6-formyl pteridine.

13. The process which comprises reacting a 2-amino-4-R^1-6-di-R-methyl-pteridine with an acylating agent to produce a 2-acylamino-4-R^1-6-di-R-methyl-pteridine, where R and R^1 are as defined in Claim 1.

14. A process as claimed in Claim 13, carried out in a liquid medium comprising an excess of the acylating agent.

15. A process as claimed in Claim 13 or 14, carried out at the reflux temperature.

16. A process as claimed in any one of Claims 13—15, which comprises reacting 2-amino-4-hydroxy-6-diethoxymethyl - pteridine with propionic anhydride to produce 2-prop-ionamido-4 - hydroxy - 6 - diethoxymethyl-pteridine.

17. A process as claimed in any one of Claims 13—15, which comprises reacting 2-amino-4-hydroxy-6-diethoxymethyl - pteridine with acetic anhydride to produce 2-acetamido-4-hydroxy-6-diethoxymethyl-pteridine.

18. A process as claimed in any one of Claims 13—17, in which the 2-amino-4-R^1-6-di-R-methyl-pteridine has been prepared by reacting the corresponding 2-amino-4-R^1-6-di-R-methyl-5,6-dihydro-pteridine with a mild oxidizing agent, R and R^1 being as defined in Claim 1.

19. A process as claimed in Claim 18, in which the mild oxidizing agent is hydrogen peroxide acting in the presence of a ferrous salt, or is air, oxygen, or iodine.

20. A process as claimed in Claim 18 or 19, in which the reaction with the mild oxidizing agent is carried out in an alcohol, a glycol, acetone, benzene, formamide, dioxane, or water.

21. A process as claimed in Claim 20, carried out at a pH of about 8 to 9.

22. A process as claimed in Claim 18, in which 2-amino-4-hydroxy-6-diethoxymethyl-5,6-dihydropteridine has been converted to 2-amino-4-hydroxy-6 - diethoxymethyl-pteridine by the action of hydrogen peroxide acting in the presence of ferrous chloride.

23. A process as claimed in Claim 18, in which 2-amino-4 - hydroxy-6 - dibenzyloxy-methyl-5,6-dihydropteridine has been converted to 2-amino-4-hydroxy-6-dibenzyloxy-methyl-pteridine by the action of hydrogen peroxide acting in the presence of ferrous sulphate.

24. A process as claimed in any one of Claims 18—23, in which the 2-amino-4-R^1-6-di-R-methyl-5,6-dihydropteridine has been prepared by condensing a 2 - halo-3,3-di-R-propionaldehyde with a 2,4,5-triamino-6-R^1-pyrimidine, R and R^1 being as defined in Claim 1.

25. A process as claimed in Claim 24, in which the condensation is carried out in the presence of a solvent comprising water, an alcohol or glycol, acetone, benzene, or form-amide, and a condensing agent.

26. A process as claimed in Claim 25, in which the condensing agent is sodium acetate, disodium phosphate, silver carbonate, or sodium formate.

27. A process as claimed in any one of Claims 24—26, in which the condensation is carried out at a temperature of 60—65° C.

28. A process as claimed in Claim 24, in which 2-bromo-3,3-diethoxy-propionaldehyde has been condensed with 2,4,5 - triamino-6-benzyloxy-pyrimidine to form 2 - amino-4-benzyloxy-6-diethoxymethyl - 5,6 - dihydro-pteridine.

29. A process as claimed in Claim 24, in which 2-bromo-3,3-diethoxy-propionaldehyde has been condensed with 2,4,5 - triamino - 6-hydroxy-pyrimidine to produce 2-amino-4-hydroxy-6-diethoxymethyl-5,6 - dihydropter-idine.

30. A process as claimed in any one of

Claims 23—29, in which the 2-halo-3,3-di-R-propionaldehyde has been prepared by a process described and claimed in the specification of our copending Application No. 2842/54.

31. A process as claimed in Claim 13, when carried out substantially as described with reference to Example 4 or 5 hereinbefore.

32. A process as claimed in Claim 31, in which the starting material has been prepared substantially as described with reference to Example 2 hereinbefore.

33. The process which comprises hydrolysing a 2-acylamino-4-R^1-6-di-R-methylpteridine with acid to produce the corresponding 2-acylamino-4-hydroxy-6-formyl-pteridine, where R and R^1 are as defined in Claim 1.

34. A process as claimed in Claim 33, carried out in solution in water or an inert organic solvent.

35. A process as claimed in Claim 33, carried out in a solvent medium comprising an excess of the acid used for the hydrolysis.

36. A process as claimed in any one of Claims 33—35, in which the acid is hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, or formic acid.

37. A process as claimed in any one of Claims 33—36, in which 2-acetamido-4-hydroxy-6-diethoxymethyl-pteridine is hydrolysed to 2-acetamido-4-hydroxy-6-formyl-pteridine.

38. A process as claimed in any one of Claims 33—37, in which the 2-acylamino-4-R^1-6-di-R-methyl-pteridine has been prepared by a process as claimed in any one of Claims 13—32.

39. A process as claimed in Claim 33, when carried out substantially as described with reference to Example 6 hereinbefore.

40. A compound as claimed in Claim 1, when prepared by a process as claimed in any one of Claims 13—32 or its obvious chemical equivalent.

41. A compound as claimed in Claim 2, when prepared by a process as claimed in any one of Claims 33—39 or its obvious chemical equivalent.

D. YOUNG & CO.,
10, Staple Inn, London, W.C.1,
Agents for the Applicants.

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